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Editorials

Diabetes and dementia

Is the brain another site of end-organ damage?

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Diabetes mellitus (DM) is an appalling disorder—quiet enough at onset, but with a toll on the body that is immense, causing damage to eyes, limbs, kidneys, and heart. Now Ott et al., in this issue of *Neurology*, provide compelling evidence that the brain too is damaged and that type 2 DM increases risk of dementia.[1] Such has been suspected for some time. Case–control and prospective studies have suggested that cognition is impaired in patients with diabetes,[2] and cross-sectional studies, including the earlier report from the Rotterdam group,[3] have suggested that diabetes is a risk factor for dementia. What was needed was large, prospective, population-based studies examining diabetes as a risk factor for dementia. The study now reported fulfills these demanding epidemiologic criteria amply, following a population of over 6,000 for up to 6 years, and demonstrating that the risk of dementia is nearly doubled in those with diabetes.

If, as seems to be the case, diabetes is responsible for causing dementia, then what is the mechanism? One obvious explanation would be that it is not the diabetes per se but the vascular complications of diabetes that result in neurodegeneration. Some earlier studies have found that diabetes increases the

risk of vascular dementia, although studies such as those tended to pass over the fact that mixed vascular and AD pathology is common and vascular dementia in the absence of AD changes is rare.[4] The Rotterdam study is unable to fully address whether the dementia associated with diabetes was vascular in origin; although only a minority had vascular dementia according to well-recognized criteria, neuroimaging was performed in only a small proportion. In any case, the distinction may not be important as it has become increasingly clear that vascular risk factors increase the risk of AD itself.[5] Ultimately, it is only with neuropathologic studies that the influence of risk factors on specific pathology can be answered, with one recent such study suggesting that diabetes does not increase the plaques and tangles of AD.[6]

Despite this, there are indications that the effect of diabetes on dementia is not, or at least not entirely, mediated through vascular factors. In the Rotterdam study, careful evaluation of cardiovascular risks was performed; these factors, although known to increase risk of dementia, did not account for a significant proportion of the risk attributable to the diabetes. In other studies, adjusting for evidence of clinical vascular disease did not obliterate the effect of diabetes on cognitive impairment.[2] In one prospective study where a hypertension–diabetes interaction was observed, this was partial—whereas some of the effects of diabetes on cognition could be attributable to coexisting hypertension, there was some evidence of memory impairment in the diabetic group independent of vascular factors.[7]

If not by vascular factors, then how does diabetes increase risk? As in much basic AD research, the problem is not one of finding potential mechanisms but of eliminating them. The demonstration that insulin resistance is associated with risk[8] is important as it might suggest that it is not the long term sequelae of diabetes, such as cardiovascular abnormalities, that results in neurodegeneration, but something to do with the action of insulin or the regulation of glucose metabolism. Perhaps the mechanism is mediated through the advanced glycation end products associated with diabetes and found in AD brain in both plaques and tangles. Alternatively, the mechanism might be mediated through insulin signaling. Neuronal insulin receptor resistance and subsequent cerebral glucose metabolism abnormalities have been suggested,[9] leading to the proposal that AD is "brain-type diabetes."[10]

However, insulin signaling regulates more than glucose metabolism. In AD, neurofibrillary tangle formation correlates with cognitive impairment and is associated with the loss of microtubules. Tangles form when the microtubule-associated protein tau self-aggregates in a highly phosphorylated form—a form that fails to bind and hence stabilize microtubules. Neuropathology suggests that the deposition of highly phosphorylated tau is one of the earliest signs of AD and cellular studies have demonstrated that in neurons one particular enzyme is predominantly responsible for this phosphorylation—glycogen synthase kinase-3ß (GSK-3ß).[11] Returning in a satisfyingly complete circle to diabetes, GSK-3ß was discovered as a downstream target of insulin signaling; insulin stimulates the PI3 kinase/protein kinase B (PKB) pathway, which in turn inhibits GSK-3ß. It follows that effective insulin signaling would be expected to reduce tau phosphorylation and increase the stability of microtubules, and in cultured neurons, this is exactly what is found.[12] Yet more exciting evidence that insulin signaling through PKB is important in AD came from the recent demonstration of an interaction between the presenilin (PS) proteins and PKB. Mutations in PS-1 causing AD decreased PKB activity leading to an increase in GSK-3ß activity.[13]

That a failure of insulin signaling and mutations in PS-1 both result in decreased inhibition of the tau-kinase GSK-3ß is intriguing. An important question raised by these studies regards the effects of insulin signaling on amyloid precursor protein metabolism, and further work will be needed to

determine the place of insulin signaling in the cascade of events between amyloid formation and tau aggregation. Other questions relate to the interaction between diabetes and genetic risk factors. No doubt the Rotterdam group will examine the interaction between *APOE* and diabetes in influencing risk, but other gene/internal–environment interactions could be important. Another putative genetic risk factor for AD is the gene encoding angiotensin converting enzyme (ACE)[14] and diabetologists have already noted that polymorphic variation in ACE predisposes to insulin resistance and influences end-organ response to diabetes.[15,16] Might ACE be a common factor between AD and diabetes?

Whether the epidemiology is linked with the molecular studies or not, one obvious conclusion from this important study might have been that a new therapeutic approach had been found. It would be marvelous if we were able to proclaim that treating diabetes could be added to reducing blood pressure as a potential preventative strategy. Unfortunately, Ott et al. find the highest risk of dementia in those receiving insulin. Being treated with insulin might simply be a surrogate marker for diabetic severity, but it does suggest that we will have to understand more of the mechanisms of this important association before the public health campaigns get going.

Footnotes

See also page 1937

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